ORIGINAL ARTICLE

Rutile phase nanoTiO$_2$ as an effective heterogeneous catalyst for condensation reaction of isatin derivatives with 1,2-diaminobenzene under solvent free conditions: A greener "NOSE" approach

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Abstract   Rutile phase of TiO$_2$ nanoparticles were readily prepared and identified as an efficient heterogeneous catalyst for the synthesis of a library of quinoxaline derivatives by condensation reaction of isatin derivatives with o-phenylenediamine under solvent-free conditions. The presented method is mild, environmentally friendly, inexpensive and highly effective to give the products in good to excellent yields. The recyclability of the catalyst is another emphasis of proposed methodology.

1. Introduction

A central objective in synthetic organic chemistry has been to develop greener and more economically competitive processes for the efficient synthesis of biologically active compounds with potential application in the pharmaceutical and related industries. In this context, nanotechnology offers the opportunity to make products and processes green from the beginning. Recently, metal/metal oxide nanoparticles as efficient heterogeneous catalysts have been used in various organic transformations (Grunes et al., 2003). The interesting features inherited with these small particle sizes are their large surface area along with more edges and corners and distinct electronic, thermal and chemical properties (Ramarao et al., 2002; Rautio et al., 2009; Reetz and Westermann, 2000).

The crucial role of nanoparticles in organic transformations is their excellent catalytic activity, straightforward recoverability, better selectivity and their versatile role in green chemistry (Cox et al., 1988; Gladysz, 2001, 2002; Pacchioni, 2000; Polshettiwar and Varma, 2010). Thus, the domain of metal nanoparticle catalysis (Fihri et al., 2012; Polshettiwar et al., 2008, 2009) should offer opportunities for mining new chemical

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reactions (Murugadoss et al., 2009; Shimizu et al., 2009; Witham et al., 2010).

TiO$_2$ nanoparticles have been widely investigated in the past decades due to their multiple potential applications (Chen and Wang, 2006; Rajalakshmi et al., 2008; Wang et al., 2007). TiO$_2$ nanoparticle catalyst as an inexpensive, non-toxic, moisture stable, reusable, commercially available white powder is of great interest to many scientists in the recent years. In general, several similar applications of this nanoscale method, as an effective catalyst in green synthetic organic chemistry, have already been highlighted in the literature (Abdolmohammadi, 2012; Hosseini-Sarvari, 2007; Kassaee et al., 2011; Lakshmi Kantam et al., 2006; Ropero-Vega et al., 2010; Shirini et al., 2011).

In the context of green chemistry (Anastas and Warner, 1998) the solvent-free approach is simple with amazing versatility. It reduces the use of organic solvents and minimizes the formation of other waste. The reactions occur under mild conditions and usually require easier workup procedures and simpler equipment. Moreover, it may allow access to compounds that require harsh reaction conditions (Martins et al., 2009; Tanaka, 2009; Walsh et al., 2007).
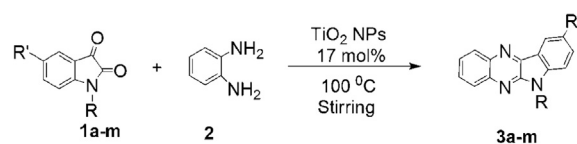
Isatin (Silva et al., 2001) and its derivatives represent an important class of 'privileged structures' (Evans et al., 1988) capable of serving as ligands for a wide range of biological targets. While, quinoxaline is a versatile nitrogen containing heterocyclic compound and has been considered as a wonder nucleus that posses a variety of biological activities, specifically as AMPA/GlyN receptor antagonists (Auberson et al., 1998; Nikam et al., 1999) angiotensin-II receptor antagonists (Kim et al., 1993a, 1993b) anti-cancer (Corona et al., 2000; Melero et al., 2004; Piras et al., 2004), anti-infection (Carta et al., 2003; Hui et al., 2006) activities. Its core structure is a part of several naturally occurring compounds such as flavor-enzymes, riboflavin, molybdopterines and antibiotics of Streptomyces (Veroni et al., 2008). The diversity in the biological response of quinoxaline derivatives has gained more attention of many researchers to explore this skeleton to its multiple potential against several diseases and pathological conditions (Patidar, 2011).

There are several methodologies reported in the literature for the condensation reaction of isatin and substituted isatins with o-phenylenediamine (Alsubari et al., 2009; Bergman et al., 2003; Ivashchenko et al., 1984; Niume et al., 1982). These protocols suffer from shortcomings such as mixture of products, prolonged reaction time, low yields, harsh reaction conditions, undesirable by products and toxicity. Therefore, to overcome these drawbacks and in our continual interest in the growth of green chemistry (Bajpai et al., 2014), we herein report "NOSE" (nanoparticles-catalyzed organic synthesis enhancement) approach for the condensation reaction of isatin derivatives with o-phenylenediamine under solvent free conditions. To the best of our knowledge, nanoTiO$_2$ catalyzed condensation reaction of isatin derivatives with o-phenylenediamine under solvent free-conditions is not yet reported.

2. Experimental

2.1. General remarks

All chemicals were procured from Aldrich, USA, and E. Merck, Germany and used as such. N-substituted isatins were

Scheme 1

prepared by earlier reported procedures. TLC was carried out on SiO$_2$ gel (HF254, 200 mesh). The solvent system employed was ethyl acetate:n-hexane (11:9) and the spots were identified by placing the plate in Iodine chamber. IR spectra were recorded on a PerkinElmer FT/IR version10.03.05 spectrometer. NMR spectra were run on a JEOL AL300 FTNMR spectrometer; chemical shifts are given in δ ppm, relative to TMS as internal standard. Elemental microanalysis was performed on Exeter Analytical Inc Model CE-440 CHN Analyzer. Melting points were measured in open capillaries and are uncorrected. An XRD spectrum was recorded on a Scifert X-ray Diffraction System. TEM image was taken from TECNAI G2, FEI. SEM image was recorded from Scanning Electron Microscope, QUANTA 200 F. BET surface area analysis was carried by Smart Sorb-93 manufactured by Smart Instruments Pvt. Ltd.

2.2. Typical procedure for the synthesis of rutile phase TiO$_2$ NPs (Sharma, 2010)

In 200 ml of double distilled ice cold water, 10 ml of TiCl$_4$ was added dropwise. The resulting mixture was stirred at room temperature. Now, 6 ml of ammonia solution was added in dropwise manner with vigorous stirring. The whole reaction mixture was stirred for 4 h, centrifuged, filtered, washed several times by ethanol, dried and calcinated at 900 °C. The synthesized TiO$_2$ NPs were characterized by XRD, TEM and FT-IR analysis.

2.3. General procedure for the synthesis of quinoxaline derivatives 3a-m

To a mixture of isatin derivatives **1a–m** (1 mmol) and o-phenylenediamine (1 mmol), 17 mol% of TiO$_2$ NPs were added (Scheme 1). The mixture was heated and stirred at 100 °C for 45 min. The progress of the reaction was monitored by thin layered chromatography (n-hexane:ethyl acetate, 1:1). After completion, 10 ml acetone was added to the reaction mixture; the catalyst was removed by filtration and washed with xylene and acetone. Then, the liquid portion was evaporated and dried. The crude products were recrystallized from ethanol. The chemical structures of all synthesized compounds were established by their spectral data.

2.3.1. Spectral data of representative compound 3a

Brown-yellow solid, IR (KBr) υ: 3400, 3090, 3019, 2960, 2849, 1660, 1614, 1567, 1484, 1323, 1210, 1169, 1005, 875, 744, 718, 633, 580 cm^{-1}. ^{1}H NMR (300 MHz, DMSO) δ: 6.80–8.23 (m, 8H, aromatic protons), 12.53 (s, 1H, NH) ppm. ^{13}C NMR (75.45 MHz, DMSO) δ: 113.6, 114.9, 117.6, 117.7, 117.8, 121.4, 123.3, 124.9, 126.3, 127.5, 128.1, 129.1, 129.2, 129.9, 130.3, 130.9, 131.1, 131.5, 138.6, 142.3, 147.7, 154.2,

154.6 ppm. Anal. Calcd for $C_{14}H_9N_3$: C, 76.70; H, 4.14; N, 19.17 Found: C, 76.73; H, 4.15; N, 19.1.

3. Results and discussion

TiO_2 NPs were characterized by XRD, TEM and FTIR analysis. It has been observed that the sample of TiO_2 NPs was highly crystalline as evident from XRD pattern in which broad peaks with high intensity extended over the 2θ scale. The peaks observed at $2\theta = 26.9°$, $35.9°$, $40.8°$, $43.3°$, $53.7°$, $62.3°$, $69.0°$ and $76.35°$ corresponding the lattice planes (110), (101), (111), (210), (211), (310), (301), (202). These peaks clearly indicate the formation of rutile phase of TiO_2 NPs (Sharma, 2010; Thamaphat et al., 2008). The broadening of peaks indicates the smaller particle size of TiO_2 NPs (Fig. 1). The average particle size has been estimated by using *Debye-Scherer formula*.

$$D = 0.94\lambda/\beta \cos\theta$$

where λ is wave length of X-ray (0.1540 nm), β is FWHM (full width at half maximum), θ is diffraction angle and D is particle diameter size. On the basis of this investigation the average particle size was found 99 nm.

Transmission electron microscopy (TEM) analysis was carried out to confirm actual particle size of TiO_2 NPs. Fig. 2 indicates the particles were agglomerated and non-homogenous. The average particle size was found 94 nm (Fig. 2).

FT-IR spectra of synthesized TiO_2 NPs showed the peaks around 3000 and 1620 cm^{-1} which arises due to the stretching and bending vibration of the –OH group. While the presence of broad peak at 666 cm^{-1} in the IR-spectrum of pure TiO_2 NPs, represents stretching vibrations of Ti–O–Ti (Fig. A, Supporting information).

Surface area analysis was done by nitrogen absorption using BET surface analyzer and the surface area was found to be 25. 32 m^2/g (Fig. B, Supporting information).

The condensation of isatin derivatives with o-phenylenediamine gives three different products (Bergman et al., 2003; Ivashchenko et al., 1984; Niume et al., 1982) depending on the reaction conditions, so the formation of selectively one of the product was our prime objective and that was achieved by using TiO_2 NPs catalyst under solvent free conditions.
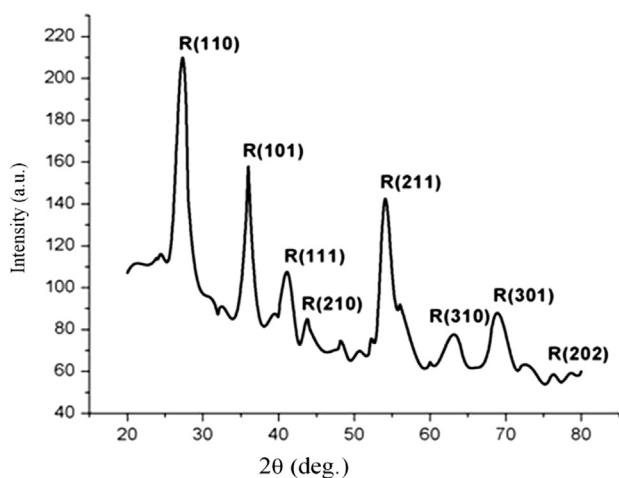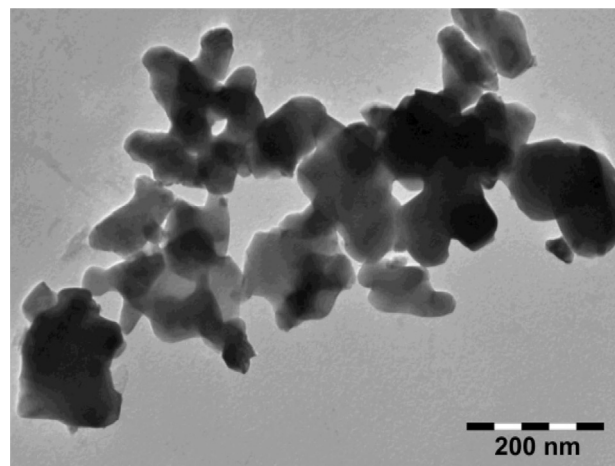

Figure 2   TEM image of TiO_2 NPs.

Condensation reaction of isatin derivatives **1a–m** with o-phenylenediamine **2** in the presence of catalytic amount of TiO_2 NPs under solvent-free conditions at 100 °C, afforded selectively quinoxaline derivatives **3a–m** in excellent yield (Scheme 1 and Table 1).

A plausible mechanism for the formation of quinoxaline derivatives is shown in Scheme 2. The reaction follows a mechanism of acid-catalyzed condensation reactions. TiO_2 coordinates with carbonyl oxygen atom of isatin derivatives, thus increasing the electrophilicity of the carbonyl carbon. Due to which partial polarization of carbonyl group takes place that results nucleophilic attack of o-phenylenediamine to carbonyl carbon atom. The resultant amino-1,2-diol readily undergoes dehydration to give quinoxaline derivative as the end product.

The chemical structures of the respective synthesized quinoxaline derivatives were established by their spectral data.
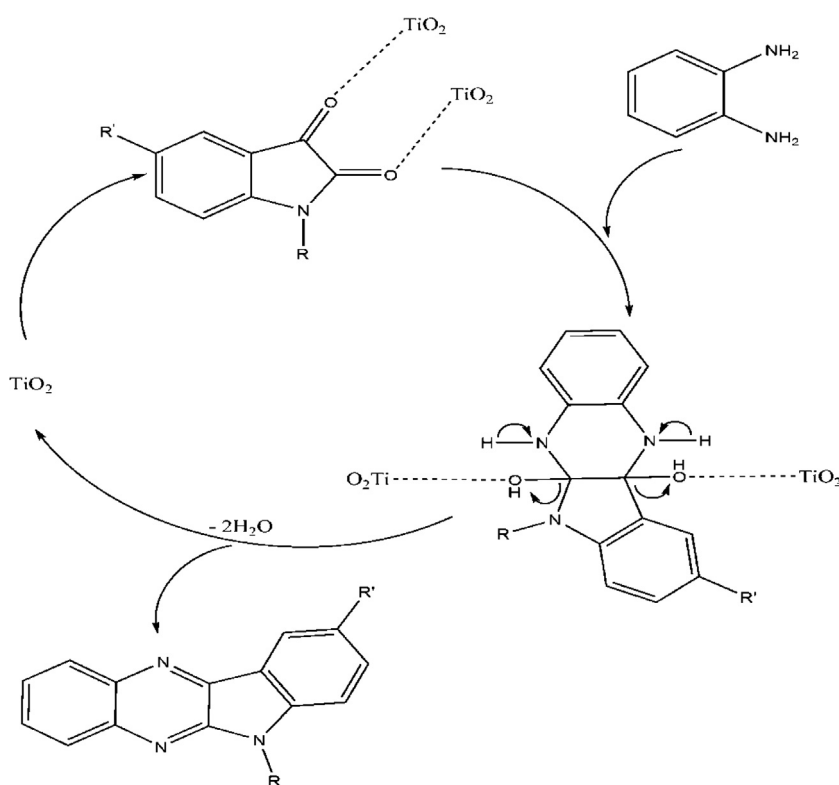
In order to find optimum reaction conditions, several parameters were investigated. Expectedly, efficiency of the catalytic system was affected by the catalyst amount. Therefore, a set of experiments using different amounts of TiO_2 NPs was taken into account for the condensation reaction of isatin with o-phenylenediamine under solvent-free condition at 100 °C (Table 2). The synthetic route was drastically dependent on the presence of catalyst and only poor yield was observed in the absence of catalyst after 120 min (Entry 1, Table 2). It was found that product yield was increased with enhancing catalyst concentration (Fig. 3). Only 5 mol% of TiO_2 NPs was sufficient to attain 55% of product yield after 80 min (Entry 2, Table 2). The best yield of 95% was obtained with 17 mol% of TiO_2 NPs (Entry 6, Table 2). However, further addition of catalyst concentration (>17 mol%) did not improve the reaction rate and product yield (Entry 7, Table 2).

The condensation reaction of isatin with o-phenylenediamine was examined under different temperatures. Obviously, reaction rate and product yield both were increased with enhancing temperature from 50 to 100 °C (Fig. 4). In contrast, at reaction temperatures above 100 °C, there is a decrease in product yield with temperature was observed. On the basis of this study, it would be concluded that the 100 °C was favorable temperature for the condensation reaction of isatin with o-phenylenediamine (Table 3).

Figure 1   XRD pattern of TiO_2 NPs.

Table 1 Reaction of isatin derivatives with *o*-phenylenediamine.[a]

Entry	R′	R	% Yield	M P (°C)
3a	H	H	95	244
3b	Cl	H	95	256
3c	H	CH$_2$CH$_3$	90	180 (Bajpai et al., 2014)
3d	Cl	CH$_2$CH$_3$	92	146
3e	H	CH$_2$CH$_2$CH$_3$	94	218
3f	Cl	CH$_2$CH$_2$CH$_3$	91	244
3g	H	CH$_2$Ph	90	176
3h	Cl	CH$_2$Ph	92	206
3i	H	COCH$_3$	88	266
3j	Cl	COCH$_3$	80	318
3k	H	CH$_2$COOEt	94	160 (Bajpai et al., 2014)
3l	Cl	CH$_2$COOEt	92	248
3m	H	CH$_2$CH$_2$CH$_2$CH$_3$	88	184 (Bajpai et al., 2014)

[a] Reaction condition: isatin derivatives, *o*-phenylenediamine (1:1) and TiO$_2$ NPs 17 mol% were stirred at 100 °C to produce solid products.

Scheme 2 Proposed mechanism for the formation of quinoxaline derivatives **3a-m**.

Table 2 Effect of TiO$_2$ NPs (mol%) on the condensation reaction of isatin with *o*-phenylenediamine.[a]

Entry	TiO$_2$ (mol%)	Time (min)	% Yield
1	0	120	40
2	5	80	55
3	10	55	75
4	12	50	82
5	15	45	89
6	17	45	95
7	20	45	95

[a] Reaction condition: isatin, *o*-phenylenediamine (1:1) and TiO$_2$ NPs were stirred at 100 °C to produce a solid product.

To investigate the effect of solvents, the condensation reaction of isatin with *o*-phenylenediamine in various organic solvents at refluxing temperature using 17 mol% TiO$_2$ NPs as the catalyst was carried out (Table 4 and Fig. 5). About 84% of the expected product **3a** was obtained when the solvent was ethanol (Entry 1, Table 4). Obviously, the polar solvents such as ethanol and acetonitrile were much better than nonpolar solvents (Entry 1 & 2, Table 4). It was observed that reaction takes more time to give high yield of product in the presence of solvent, under similar ratio of the reactants (Entry 1, 2, 3 & 4 Table 4). This may be due to the competitive adsorption of the solvent with the substrate molecule on the catalyst surface;
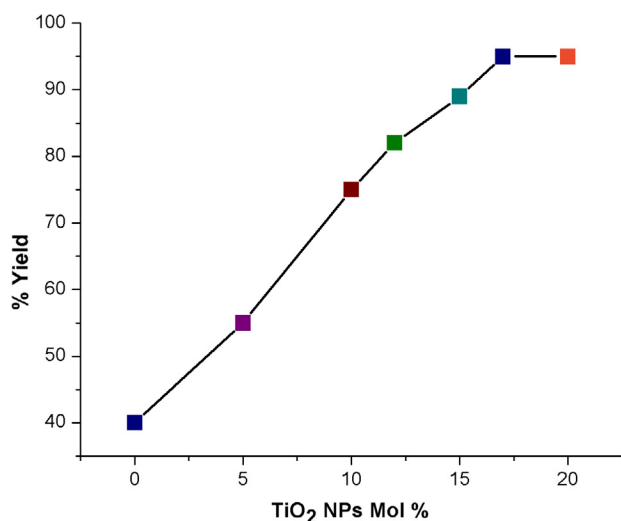
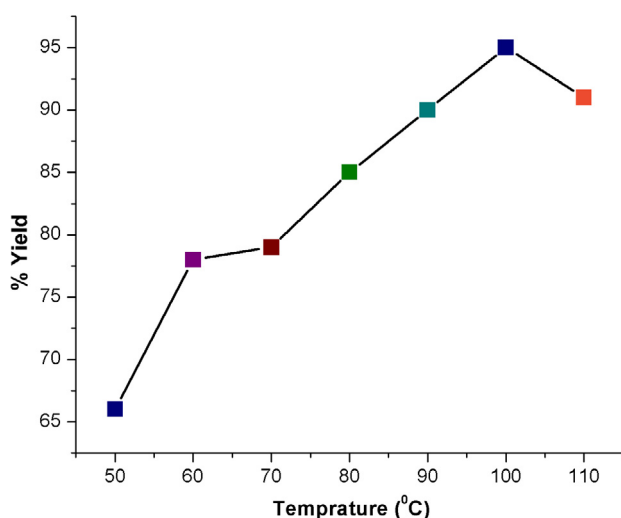**Figure 3** Effect of amount of TiO₂ NPs on the condensation reaction of isatin with *o*-phenylenediamnine.

Figure 4 Effect of temperature (°C) on the condensation reaction of isatin with *o*-phenylenediamnine.

Table 3 Effect of temperature on the condensation reaction of isatin with *o*-phenylenediamine.[a]

Entry	Temp. (°C)	Time	% Yield
1	Rt	–	No reaction
2	50	8 h	66
3	60	5 h	78
4	70	3.5 h	79
5	80	1 h	85
6	90	1 h	90
7	100	45 min	95
8	110	45 min	91

[a] Reaction condition: isatin, *o*-phenylenediamine (1:1) and TiO₂ NPs 17 mol% were stirred to produce a solid product.

hence reaction under solvent-free condition gives better yields in short time (Entry 5, Table 4). A possible explanation for

Table 4 Effect of solvents on the condensation reaction of isatin with *o*-phenylenediamine.[a]

Entry	Solvents	Time	% Yield
1	Ethanol	3 h	84
2	Acetonitrile	3 h	81
3	Xylene	3 h	72
4	Toluene	3 h	75
5	Solvent free	45 min	95

[a] Reaction condition: isatin, *o*-phenylenediamine (1:1) and TiO₂ NPs 17 mol% were stirred to produce a solid product.
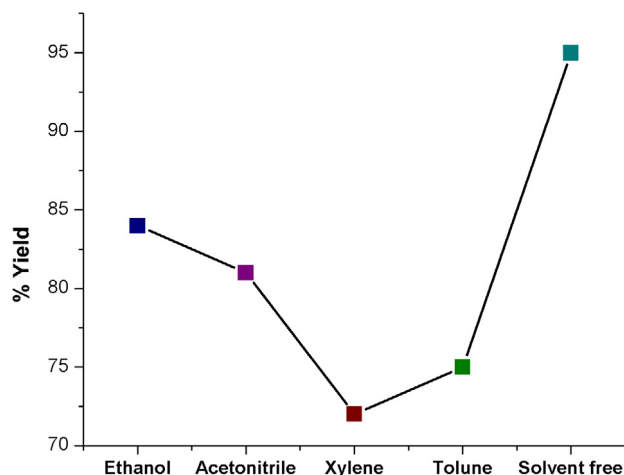

Figure 5 Effect of solvents on the condensation reaction of isatin with *o*-phenylenediamine.

Table 5 Effect of type of TiO₂ (Bulk & Nano) on the reaction of isatin with *o*-phenylenediamine.[a]

Type of TiO₂	Mol%	% Yield
	5	44
TiO₂ (Bulk)	10	53
Ave. particle size:1 μm	15	68
Surface area: 5.95 m²/g	17	73
TiO₂ (Nano)	5	55
Ave. particle size: 94 nm	10	75
Surface area: 25.32 m²/g	15	89
	17	95

[a] Reaction condition: isatin, *o*-phenylenediamine (1:1) were stirred at 100 °C to produce a solid product.

higher yield in solvent-free conditions is that the eutectic mixture having uniform distribution of the reactants which brings the reacting species in close proximity to react with each other than in the presence of solvent (Fig. 5).

The effect of type of TiO₂ (nano or bulk) was investigated in the condensation reaction of isatin with *o*-phenylenediamine under the optimized reaction conditions (Table 5). Four concentrations 5, 10, 15 and 17 mol% TiO₂ were used to study this important parameter. These data proved that particle size and surface area would be an important factor for the catalytic efficacy of the TiO₂ NPs (Table 5 & Fig. 6) (Figs. B, C and D Supporting information).
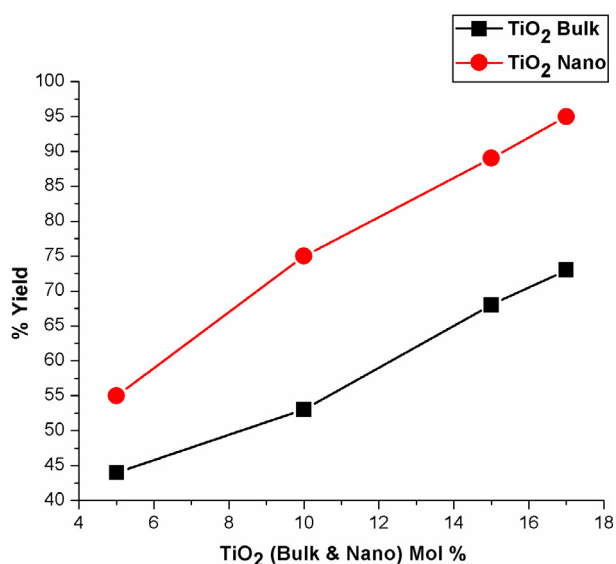
Figure 6 Effect of type of TiO$_2$ (Bulk & Nano) on the condensation reaction of isatin with *o*-phenylenediamine.

Figure 7 Reusability and recyclability of TiO$_2$ NPs catalyst for the condensation reaction of isatin with *o*-phenylenediamine.

The reusability of TiO$_2$ NPs was examined under optimized reaction conditions (Table 7). The catalyst was separated by filtration, washed, dried and reused for a fresh reaction mixture up to run no. 4. The results showed that there is no appreciable decrease in product yield in subsequent reuse which proves the reusability and recyclability of TiO$_2$ NPs (Fig. 7).

Table 6 Effect of different catalysts on the condensation reaction of isatin with *o*-phenylenediamine.[a]

Type of catalyst	Mol%	Time (min)	% Yield
Bentonite clay	20	60	77
K-10 clay	20	60	77
PTSA	30	75	65
NH$_4$Cl	30	75	72
EDTA	40	75	60
Iodine	20	60	72
Yb(OTf)	20	60	80
TiO$_2$ (Nano)	17	45	95

[a] Reaction condition: isatin, *o*-phenylenediamine (1:1) at 100 °C were stirred to produce a solid product.

4. Conclusion

A novel synthetic route has been developed for the condensation reaction of isatin derivatives with *o*-phenylenediamine using TiO$_2$ nanoparticles under solvent free conditions. The yield of the products was obtained up to 95% at 100 °C. The advantage of proposed method is its facile reaction conditions, the product can be isolated very easily without the use of column chromatography and the catalyst is recyclable. The simplicity of the present protocol makes it an interesting alternative to other approaches. The catalyst is expected to contribute to the development of environmentally benign methods and forms a part of the nanomaterial chemistry.

Table 7 Reusability and recyclability of TiO$_2$ NPs catalyst.[a]

Entry	Number of cycle	% Yield
1	–	95
2	1	95
3	2	94
4	3	92
5	4	89

[a] Reaction condition: isatin, *o*-phenylenediamine (1:1) and TiO$_2$ NPs 17 mol% were stirred at 100 °C to produce a solid product.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arabjc. 2014.11.037.

A comparison of the efficiency of catalytic activity of the TiO$_2$ NPs with several other catalysts is presented in Table 6. Reaction of isatin with *o*-phenylenediamine was taken into account and the comparison was in terms of mol% of catalyst, reaction time, and percentage yield. The result showed that TiO$_2$ NPs were the best catalyst in terms of mol%, reaction time, and percentage yield. Although some of the catalysts led to good yield, some of them are environmentally hazardous and require longer reaction times and higher mol% of catalysts (Table 6).
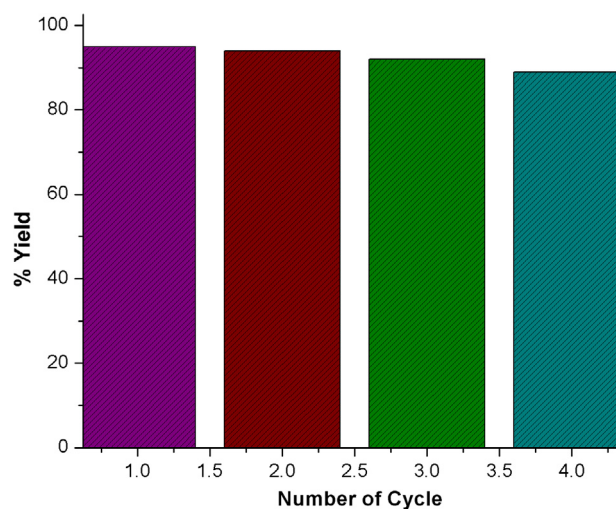
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